REMARKS

In the Office Action dated August 17, 2001, the Examiner indicated the previously filed reply (dated May 4, 2001) was a non-responsive reply because the amendment filed on April 30, 2001, (paper 25) failed to meet the requirements of 37 CFR 1.121. As specified by the Examiner, said amendment has been treated as unentered. Applicants are herein providing a further amendment and respectfully request that the amendment be made of record.

Applicants filed with the request for reconsideration dated April 30, 2001, a Sequence Listing, and it is assumed that unless specifically notified otherwise this submission was acceptable.

Status of the Application.

Claims 14 and 17 - 28 are pending with entry of the instant amendment. Claims 17 - 28 are new. Claim 13 has been canceled. However, new independent claim 18 corresponds to canceled claim 13. Claim 18 further recites steps in identifying the T-cell epitope and support is found at page 25 of the specification. Claim 19 is dependent on claim 18 and further defines the protein as a protease. Claim 14 has been amended to depend from claim 18. New claim 17 is an amended version of original claim 12. New claim 20 is an independent claim directed to a method of reducing the allergenicity of a microbial subtilisin. Claims 21 - 23 depend from claim 20, and support for the claims is found in examples 1 and 2, original claim 14, and at page 13 of the specification. Claims 24 - 28 depend from claim 14. New matter has not been added by these amendments.

New claim 17.

New claim 17 is essentially identical to claim 12 of the originally filed application as well as its divisional application serial no. 09/255,505 as amended in paper 10 (Amendment and Request for Reconsideration mailed June 16, 2000).

During an interview dated March 6, 2001, which included Examiner Saunders and Patent Attorney Susan Faris, it was suggested that, because the remaining issues in the prosecution of claims 13, 14 and 12 of the copending application were the same,

the claims be recombined in this application. See Paper 22 (Interview Summary). The application corresponding to USSN 09/255,505 has been abandoned.

Rejections under 35 U.S.C. §103.

In the previous office action, the Examiner rejected claims 13 and 14 under 35 U.S.C. §103(a) as allegedly being unpatentable over Garman *et al.* (5,820,862) in view of Bhardwaj *et al.* (J. Clin. Invest. 1994) and Mackay *et al.* (5,648,219). The Examiner also rejected claim 12 in the co-pending application, serial no. 255,505, as allegedly obvious under 35 U.S.C. §103(a) over Worthington, *et al.*, in view of Bhardwaj, *et al.* and further in view of Schuler, *et al.* and/or Mackay, *et al.* (New claim 17 corresponds to claim 12). Applicants respectfully traverse the above stated rejections, and incorporate the arguments made herein of record in earlier filed responses.

In considering obviousness, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To establish a prima facie case of obviousness, the Examiner must cite prior art which discloses each element of the claims unless the element would be obvious to one of skill in the art. The Examiner must also provide reasons or motivation for one of skill to carry out the claimed method and demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting in carrying out the method. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991).

Garman *et al.* is cited for teaching the identification of T-cell epitopes within a protein allergen and the medication thereof to provide peptides which induce a lowered or not any proliferative response. It is recognized by the Examiner that Garman *et al.* fail to teach the use of naive T-cells. Rather it teaches epitope screening with T-cells from sensitized individuals. All of Applicants' claims are directed to using naïve donors as a source of T-cells.

Additionally, Applicants highlight that Bhardwaj *et al.* does not teach obtaining CD+4 or CD+8 T-cells from naïve individuals, but is concerned with infected DCs. At page 799, second column, Bhardwaj *et al.* state: "Because CTL activity was measured on influenza A/PR8-infected targets, a strain first identified in 1934, and the prevalent strains are A/Texas/36/91 and A/Beijing/232/92, the CTLs generated appear to be cross-reactive, confirming other studies of human influenza-specific CTLs. Most donors,

>90%, could be stimulated to form CTLs with virus-infected dendritic cells, indicating that the majority of our donor pool has been exposed to influenza."

This cross-reactivity indicated the donors were sensitized to influenza and were, in fact, not naïve. As stated above, Applicants' claims are directed to using naïve donors as a source of T-cells. Moreover, it would not have been obvious to one of ordinary skill in the art to use T-cells from a naïve donor as one skilled in the art would not have had a reasonable expectation of success in doing so.

The Examiner has cited Mackay *et al.* for teaching the obtaining of immortal DCs via the use of a differentiation inducing medium having constituents such as GM-CSF as a major one. Further the Examiner states Mackay *et al.* teach that the obtained DCs can be used for epitope mapping by testing with a large number of synthetic peptides (col. 9, line 16+), and that like Bhardwaj *et al.*, Mackay et al. teach DCs are the most important antigen presenting cell type and that they can present to naive T-cells (col. 1, lines 53 and col. 9, lines 34).

While Mackay *et al.* may disclose that GM-CSF should be added to a growth medium for DCs, and further that DCs can take up, process and present exogenous antigens and therefore maybe used as a tool to identify epitopes along with synthetic peptides, there is no teaching or suggestion as to the method claimed by Applicants. Applicants contend the naïve T-cells described by Mackay *et al.* were only used in a mixed lymphocyte reaction (See Example VII). Moreover the definition of an activated dendritic cell, as used by Mackay *et al.*, is one that is a more mature dendritic cell that expresses high levels of MHC class II, ICAM-1 and B7-2, and is capable of stimulating the proliferation of naïve allogenic T cells in a mixed leukocyte reaction. The use of naïve T-cells to generate a primary response to dendritic cells primed with antigen is not described or suggested by the reference. Furthermore, Mackay concerns the isolation of DCs. The isolated DCs according to the reference result in an immortalized cell line, designated JAWII. Applicants are not claiming the use of a cell line.

Even if one skilled in the art were to combine the cited references the claimed method would not be made obvious. There is no suggestion in the references that one should use naive T-cells and DCs in the manner claimed by Applicants.

In addition to the references cited above, the Examiner has rejected claim 12 (now claim 17) over Worthington *et al.* and Schuler *et al.* Worthington, *et al.* is cited for

identification of T-cell epitopes by contacting peptide fragments of a protein by contacting the peptides with T-cells, and Schuler *et al.* is cited for the differentiation of dendritic cells. The Examiner concludes that motivation to combine the references would have been to gain the advantage of being able to use blood samples from naive individuals instead of immunized individuals.

While arguably the cited references may disclose parts of the claimed invention, the invention as a whole is neither disclosed nor suggested by the cited references individually or in any combination. While Schuler *et al.* may teach the differentiation of DCs, the reference lacks any teaching concerning the use of DCs in the manner recited by Applicants.

Applicants thus assert that no reference teaches or suggests the use of naïve donors as the source of peripheral blood cells. In fact, according to the collective dogma (as reflected in the references cited by the Examiner), one can not map T cell epitopes on a large scale such as done in the assay of the present invention without clones, cell lines or T cells from exposed individuals.

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7620.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDED CLAIMS

14.(Twice amended) The method according to **[claim 13]** **claim 18**, wherein said epitope is modified by:

(a) substituting the amino acid sequence of the epitope with an analogous sequence from a human homolog to the protein of interest;

(b) substituting the amino acid sequence of the epitope with an analogous sequence from a non-human homolog to the protein of interest; or

(c) substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope.